Remarks

The Amendments

Claims 1, 7, 11, 15, 39, 43, 45, and 47 have each been amended to state that Applicants' composition comprises a dispersion, which in turn comprises spray dried particles that are solidified in less than 5 seconds and that have a residual solvent content less than 10 wt%. Support is in the application at page 16, lines 14 and 25-26.

Claims 1, 7, 11, 15, 39, 43, 45, and 47 have each also been amended to state that the drug in the dispersion is molecularly dispersed and amorphous. Support is in the application at page 7, lines 26-28 and page 11, lines 12, 19 and 24-25.

New claims 49, 50, 51, and 52 have been added and state, respectively, that the dispersion particles are solidified in less than 2 seconds, that the particles have a residual solvent content less than 2 wt%, that the particles are spray-dried from a solution in which the concentration of drug in the solvent is less than 20g/100g and in which the total solids content is less than 25 weight %, and that the drug:polymer weight ratio is greater than 1 to 20 and less than 1 to 0.4. Support is in the specification at page 16, lines 14-15, page 16, line26, page 4, lines 20-22, and page 13, line 27 (as amended by Applicants' amendment dated November 24, 2003).

Claim 27 has been deleted to improve form since it was redundant.

The invention

Applicants' claims are directed, *inter alia*, to a composition comprising a spray dried dispersion of a sparingly water-soluble drug and HPMCAS. As stated in the specification, rapid (yet thorough) drying is critical to the spray dried particles maintaining a uniform, homogeneous composition instead of separating into drug-rich and polymer-rich phases, and Applicants' claims now reflect preferred requirements that aid in achieving such drying. Rapid drying and low residual solvent levels are important because they can affect the quality of the resulting dispersion, as explained in the specification starting at page 15, line 31,

in terms of both the degree of concentration enhancement and the dispersion's stability with time. High residual solvent contents and long solidification times can result in phase separation and the formation of relatively pure drug domains, with the result, over time, that concentration enhancement and therapeutic efficacy can be altered. The importance of rapid drying was previously reflected in Applicants' requirement that the dispersion be homogeneous. That importance is now further reflected in Applicants' requirement for the drug to be molecularly dispersed, for the spray-dried particles to be solidified in less than 5 seconds, and for the residual solvent content to be less than 10 wt%. These features are important because (1) they are important to the invention, as discussed above and (2) neither of the references, Yamaguchi and Miyajima, discloses or otherwise describes them.

The rejections and Applicants' traversal

Claims 1, 4-7, 10, 11, 13, 15, 17, 22, 27, 39, 41-43, and 47 stand rejected under 35 USC §102(b) as being anticipated over Yamaguchi et al. The examiner stated, in pertinent part:

> Yamaguchi studies the solubility of solid dispersions of 4-O-(4-methoxyphenyl)acetyltylosin (MAT) in carboxymethylethylcellulose (CMEC) or hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT®), and using the solid dispersions an increase of AUC and Cmax of greater than 2.5 fold was observed achieved (abstract). Yamaguchi prepares solid dispersions of MAT in CMEC, AQOAT or EC (ethylcellulose) by spray drying (item#2 of page2); the solubility of crystalline MAT is determined to be 0.002 at pH 6.8 (item 1 of page 4 and Table 1). IN figure 2 and at pH 4.0, Yamaguchi shows solid dispersions of MAT and CMEC or AQOAT in a ratio of 10:1 and concentration of the MAT in a use environment from AQOAT carrier matrix is about 650 μg and the concentration of amorphous MAT without a polymer in a use environment is about 220 μg; the ratio of the MAT from the AQOAT matrix to a control, such as the one without a polymer is at least greater than 1.5 and specifically about 2.95 (see page 5 and data extrapolated from Figure 2). Although, Yamaguchi exemplifies the dissolution studies with CMEC, the Yamaguchi reference also discloses MAT with AQOAT as is seen in the abstract, pages 2 (last line) and 5, and Figure 2. MAT bulk powder is used in the study in the preparation of the solid dispersion (page 2, item #1) and powder reads on amorphous. Yamaguchi describes oral

> administration, fed state (i.e. "withholding food from the beagles from the night before the study") and measuring of blood concentration (page 4, item #7 and page 10, item #4), which description confers the implication of gastrointestinal tract environment and thus, this aspect of the disclosure reads on gastrointestinal tract use environment. Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQOAT dispersion. The carriers are different but equivalent in the Yamaguchi disclosure and the drug is the same MAT. The teachings of Yamaguchi meet the limitations of the claims. [Pages 2-3 of the July 13, 2004 Office Action]

The rejection is traversed on the basis that Yamaguchi does not disclose all elements of Applicants' invention. Each of the independent claims contains the following elements - - that the drug is molecularly dispersed, that the drug is amorphous in the dispersion, that the spray dried particles are solidified in less than 5 seconds, and that the residual solvent content is less than 10 wt%. Yamaguchi fails to disclose or describe any of these requirements.

An additional element missing from Yamaguchi is reflected in Applicants' requirement, previously present in the independent claims, that the drug-to-HPMCAS weight ratio be within the range of 1 to 0.2 to 1 to 100, i.e., between 5:1 and 1:100 in terms of whole numbers. The highest proportion of drug by weight that can be present in Applicants' dispersions is, therefore, a dispersion having a drug:polymer ratio of 5 (drug) to 1 (HPMCAS), i.e., a drug/HPMCAS dispersion containing 83% drug by weight. Yamaguchi never disclosed a drug/HPMCAS dispersion within the weight ratio range stipulated by Applicants. Yamaguchi only disclosed a MAT/AQOAT composition having a weight ratio of 10:1, i.e., above Applicants' upper limit of 1:0.2. See Yamaguchi's Figure 2.

Because so many elements required by Applicants' claims are missing from Yamaguchi, Applicants cannot be anticipated. Gechter v. Davidson, 43 USPQ2d 1030 (Fed. Cir. 1997).

> Under 35 USC §102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim. [43 USPQ2d at 1032].

It is noted that at page 3 of the Office Action, the Examiner seemed to acknowledge that Yamaguchi does not disclose a composition having all the elements required by Applicants' claims, yet the Examiner still maintained that Yamaguchi anticipates, supporting her position by reference to Yamaguchi at page 10, as follows:

> Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQOAT dispersion.[Office Action, Page 3]

First, Applicants do not agree that the characteristics of Yamaguchi's MAT/CMEC composition can be imputed to Yamaguchi's other compositions to formulate an anticipation rejection. It is emphasized that to anticipate, a reference must disclose or describe all of the elements of an Applicant's claims. See, for example, Akzo N. V. v. International Trade Commission, 1 U.S.P.Q. 2d 1241 in which a claimed process for making aramid fibers using "a solvent consisting essentially of sulfuric acid of at least 98% concentration..." was held not to be anticipated by a prior art reference calling for the use of sulfuric acid. In Akzo, the Court of Appeals for the Federal Circuit additionally accepted the ITC's finding that concentrated sulfuric acid is not inherently 98% sulfuric acid to one skilled in the art. In the same fashion, Yamaguchi fails to disclose or otherwise describe a composition exhibiting Applicants' requirements discussed above - - solidification time, residual solvent content, drug:HPMCAS ratio and that the dispersion be homogeneous and the drug molecularly dispersed therein. The Examiner has provided no basis otherwise that any of the missing elements is inherent.

Newly added claims 49-52 each further states a preferred embodiment of one or more of the requirements stated above, and none of the embodiments is disclosed or described in Yamaguchi. Thus each of the requirements stated in

these new claims, i.e., that the solidification time is less than 2 seconds (claim 49), that the residual solvent content is less than 2 wt % (claim 50), that the concentration of drug is less than 20g/100 g of solvent and the total solids content is less than 25 wt% (claim 51), and that the drug:polymer weight ratio is greater than 1 to 20 and less than 1 to 0.4 (claim 52), represents an embodiment that is not disclosed in Yamaguchi and that further patentably distinguishes each claim therefrom.

It is, accordingly, clear that Yamaguchi does not disclose Applicants' invention. The composition referred to by the Examiner in item #4 doesn't even contain HPMCAS; rather, it discloses MAT/CMEC. Nor is the drug:polymer ratio disclosed in item #4 within the range that Applicants require. Nor does Yamaguchi disclose any of the other requirements discussed above - - particles having the required solidification times and the required maximum residual solvent level, in which the drug is molecularly dispersed and amorphous. Because Yamaguchi does not disclose a composition having all of the elements required by Applicants, Yamaguchi cannot anticipate Applicants' claims.

Withdrawal of the rejection under 35 USC §102(b) over Yamaguchi is accordingly respectfully requested.

It is noted that no obviousness rejection under 35 USC §103 over Yamaguchi was made. Applicants' agree that their invention would not be obvious over Yamaguchi, on the basis that an invention cannot be obvious over a reference that fails to disclose, suggest or enable many of the elements comprising it.

Claims 1, 7, 11, 13, 15, 27, 39, 41-43, 45 and 47 were rejected under 35 USC 102(b) as being anticipated by Miyajima et al. (US 4,983,593).

> Miyajima discloses a pharmaceutical composition that comprises 5-(5,5-dimethyl-1,3,2-dioxaphosphorinane-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-itrophenyl)-3-pyridine carboxylic acid 2-(phenylmethyl)amino) ethyl ester P-oxide hydrochloride-thanol (NZ-105) and hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT) in a 1:1 ration (abstract) and column 4, lines 6-8 discloses NZ-105/HPMCAS composition where the amount o the HPMCAS is 1-7 parts by weight per unit of NZ-105. Miyajima's composition further comprises filers, binders, lubricants and disintegrants (column 4, lines 22-47). Miyajima's

composition is formulated as powders, granules, tablets, capsules or pills (column 4, lines 16-21). Powder or particles of NZ-105 and HPMCAS are produced by vacuum drying, spray drying or freeze-drying (column 3, lines 55-60). While nicardipine and nifedipine are disclosed by Miyajima in the background section as well known 1,4-dihydropyridine-type compounds that are poorly soluble in water and can be prepared as amorphous formulations, the nicardipine and nifedipine are different compounds from the compounds recited in instant claims 29, 30, 32, 34 and 36. Instant claim 37 recited nifedipine as a drug.

Examples 1-4 of Miyajima disclose NZ-105/HPMCAS composition where the ratio of the NZ-105 to the HPMCAS is 1:3. Miyajima is silent with respect to the solubility of the drug NZ-105 in a use environment or oral administration or administration to a fasted animal. However, the solubility of the drug is an inherent property of a drug and would appear to be an inherent property of the NZ-105/HPMCAS compositions. It is noted that no specific drug is claimed in the claims in question. Thus, Miyajima meets the limitations of the claims. [Pages 3-4 of the Office Action]

The rejection, although not agreed with for the claims as they existed prior to the present amendments, is believed to be obviated in view of Applicants' amendments. Each of Applicants' claims requires that the drug is molecularly dispersed, that the drug is amorphous in the dispersion, that the spray dried particles are solidified in less than 5 seconds, that the residual solvent content is less than 10 wt%, and that the drug-to-HPMCAS weight ratio is within the range of 1 to 0.2 to 1 to 100. Clearly, and for reasons that parallel those given above in traversing Yamaguchi, Miyajima fails to disclose or describe multiple elements of Applicants' claims.

Miyajima mentions the phrase "spray drying" once in his entire disclosure. Miyajima never otherwise discloses or describes anything relating to a spray drying process, or to the characteristics of any spray-dried dispersion. Miyajima fails to disclose anything relating to a solidification time of less than 5 seconds or to any limits relating to residual solvent content. Further, Miyajima fails to disclose that his drug must be amorphous in the dispersion. Indeed, Miyajima produced NZ-105 as crystals in his Reference Example 1. Nowhere does Miyajima disclose that his specific drug in a spray-dried drug/polymer composition would necessarily or inherently be amorphous. In this regard, Applicants note that a drug does not automatically become amorphous (i.e., non-crystalline) simply by spray drying. See Attachment 1 hereto ("Remington: The Science and Practice of Pharmacy", 20th Edition, Edited by Alfonso R. Gennaro,

Published by Lippincott Williams & Wilkins) which, in reference to spray drying, states:

> The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal.

Clearly a spray dried crystalline drug/polymer composition may, or may not, be amorphous, depending on the process conditions. Remington just as clearly supports that a drug in a spray dried composition can be crystalline as well as amorphous. The non-disclosure in Miyajima of a spray dried drug being amorphous constitutes an additional missing element and another reason why Miyajima does not anticipate the invention.

Withdrawal of the rejection under 35 USC §102(b) over Miyajima is accordingly respectfully requested.

Claims 23-26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (US 4,983,593). The Examiner stated, in pertinent part:

> Miyajima discloses the instant composition that comprises a sparingly water-soluble drug and HPMCAS. Although Miyajima discloses that the composition is preparable as particles, Miyajima fails to disclose particle sizes. It is also noted that there is no demonstration in applicants' specification that the recited particle sizes provide unusual results. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a pharmaceutical composition comprising NZ-105 and HPMCAS and spray dried to form amorphous dispersed solid particles. One having ordinary skill in the art would have been motivated to prepare particles of a formulation containing NZ-105 and HPMCAS with the expectation that the NZ-105 would be more soluble and in the absence of unexpected result, the particle size recited does not distinguish the instant claims over the prior art.

Claims 23-26 are all dependent claims; hence they incorporate all the features of the independent claims from which they depend. As stated above, Miyajima utterly fails to disclose anything about spray drying other than the single occurrence (column 3, line 58) where he mentions the phrase "spray drying" per se. But, Miyajima never mentions any of the other features also required by Applicants' claims. In order for an obviousness rejection to lie, the prior art must

in some way supply a suggestion to do that which Applicant has invented, and must also provide a reasonable expectation of success. . American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Realizing that Section 103 applies to the invention as a whole, and realizing that Miyajima fails to suggest several of the elements present in Applicants' claims, obviousness is untenable. An invention is simply not obvious over a reference that fails to disclose or describe (or even mention) many of its elements.

Claim 38 was rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (US 4,983,593).

> Miyajima discloses the instant composition that comprises a sparingly water-soluble drug and HPMCAS. Although Miyajima in the background section discloses nifedipine as poorly water-soluble drugs, whose solubility can be improved, Miyajima's disclosed composition does not contain nifedipine. It would have been obvious to one or ordinary skill in the art at the time the invention was made to prepare a composition that contains NZ-105 and HPMCAS. One having ordinary skill in the art would have been motivated to prepare a composition that contains nifedipine and HPMCAS according to the suggestion of Miyajima with the expectation of improving the solubility of nifedipine. [Office Action, page 5]

The rejection is traversed for the same reasons as those discussed above in discussing the rejection of claims 23-26. First, an obviousness rejection based on Miyajima must fail because Miyajima doesn't satisfy either requirement of an obviousness rejection - - it neither suggests making an HPMCAS/nifedipine dispersion nor provides an expectation of success, i.e., that such a dispersion

would solve the low solubility of nifedipine. American Hospital Supply Corp. v. Travenol Laboratories, Inc., supra. Second, claim 38 is dependent and accordingly incorporates all of the features required by the claim(s) from which it depends. But, Miyajima in no way suggests any of the other multiple limitations required by those claims.

Withdrawal of both rejections under 35 USC §103(a) over Miyajima is accordingly respectfully requested.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Applicants authorize any fees for the newly added claims to be charged to Deposit Account No. 16-1445. The Commissioner is hereby authorized to charge any additional fees which may be required, or to credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

Date: December 13, 2004

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ATTACHMENT A

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CHAPTER 37

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently, this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, and suspensions, powders also occur as a pharmaceutical dosage form. Although the use of powders as a dosage form has declined, the properties and behavior of finely divided solid materials are of considerable importance in pharmacy.

This chapter is intended to provide an introduction to the fundamentals of powder mechanics and the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

PRODUCTION METHODS

Molecular Aggregation

PRECIPITATION AND CRYSTALLIZATION

The precipitation and crystallization processes are fundamentally similar and depend on achieving three conditions in succession: a state of supersaturation (super cooling in the case of crystallization from a melt), formation of nuclei, and growth of crystals or amorphous particles.

Supersaturation can be achieved by evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, production of additional solute as a result of a chemical reaction, or a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from 10 to a few hundred molecules having the spatial arrangement of the crystals that will be grown ultimately from them.

Such small particles are shown by the Kelvin equation to be more soluble than large crystals; therefore, they require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form often highly depends on impurities in solution, pH, rate of stirring, rate of cooling, and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

SPRAY-DRYING

Atomization of a solution of one or more solids via a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed *spray-drying*. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced, and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle-Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing, and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping.

Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. How-

ever, these materials do differ considerably in melting point, brittleness, hardness, and moisture content, all of which affect the ease of particle-size reduction and dictate the choice of equipment. The heat generated in mechanical grinding, in particular, presents problems with materials that tend to liquefy or stick together and with the thermolabile products that may degrade unless the heat is dissipated by use of a flowing stream of water or air. The desired particle size, shape, and size distribution also must be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal, more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

FRACTURE MECHANICS

Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with consequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally plastic material would not rebound nor would it fracture.

The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been developed well to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction, and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

Although the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors also must be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which often is related to abrasiveness, also must be considered. This usually is measured on the Moh's scale.

Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, such as plant products, require a cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates often will release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

METHODS AND EQUIPMENT

When a narrow particle-size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle-Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Over-milling, with its subsequent production of fines, thereby is minimized. Equipment also has been designed to combine the sieving and milling steps into a single operation (see *Centrifugal-Impact Mills and Sieves*).

To avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials that are chemically and mechanically compatible with the substance being processed. The equipment should be easy to disassemble for cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction, and operation and suitable feed and outlet capacities are additional considerations in equipment selection.

Although there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw, gyratory, roll, and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters, disk, hammer, roller, and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid-energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are employed ordinarily where the size of the feed material is relatively large, ranging from 1½ to 60 inches in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products that fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, although often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle-size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed-size distribution line-matrix yields the predicted output-size distribution.

INTERMEDIATE AND FINE GRINDING MILLS

The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.